Apixaban with antiplatelet therapy after acute coronary syndrome

Alexander, J H ; Lopes, R D ; James, S ; Kilaru, R ; He, Y ; Mohan, P ; Bhatt, D L ; Goodman, S ; Verheugt, F W ; Flather, M ; Huber, K ; Liaw, D ; Husted, S E ; Lopez-Sendon, J ; De Caterina, R ; Jansky, P ; Darius, H ; Vinereanu, D ; Cornel, J H ; Cools, F ; Atar, D ; Leiva-Pons, J L ; Keltai, M ; Ogawa, H ; Pais, P ; Parkhomenko, A ; Ruzyllo, W ; Diaz, R ; White, H ; Ruda, M ; Geraldes, M ; Lawrence, J ; Harrington, R A ; Wallentin, L

Abstract: Background: Apixaban, an oral, direct factor Xa inhibitor, may reduce the risk of recurrent ischemic events when added to antiplatelet therapy after an acute coronary syndrome. Methods: We conducted a randomized, double-blind, placebo-controlled clinical trial comparing apixaban, at a dose of 5 mg twice daily, with placebo, in addition to standard antiplatelet therapy, in patients with a recent acute coronary syndrome and at least two additional risk factors for recurrent ischemic events. Results: The trial was terminated prematurely after recruitment of 7392 patients because of an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events. With a median follow-up of 241 days, the primary outcome of cardiovascular death, myocardial infarction, or ischemic stroke occurred in 279 of the 3705 patients (7.5%) assigned to apixaban (13.2 events per 100 patient-years) and in 293 of the 3687 patients (7.9%) assigned to placebo (14.0 events per 100 patient-years) (hazard ratio with apixaban, 0.95; 95% confidence interval [CI], 0.80 to 1.11; P=0.51). The primary safety outcome of major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) definition occurred in 46 of the 3673 patients (1.3%) who received at least one dose of apixaban (2.4 events per 100 patient-years) and in 18 of the 3642 patients (0.5%) who received at least one dose of placebo (0.9 events per 100 patient-years) (hazard ratio with apixaban, 2.59; 95% CI, 1.50 to 4.46; P=0.001). A greater number of intracranial and fatal bleeding events occurred with apixaban than with placebo. Conclusions: The addition of apixaban, at a dose of 5 mg twice daily, to antiplatelet therapy in high-risk patients after an acute coronary syndrome increased the number of major bleeding events without a significant reduction in recurrent ischemic events. (Funded by Bristol-Myers Squibb and Pfizer; APPRAISE-2 ClinicalTrials.gov number, NCT00831441.).

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ORIGINAL ARTICLE

Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome

John H. Alexander, M.D., M.H.S., Renato D. Lopes, M.D., Ph.D., Stefan James, M.D., Ph.D., Rakhi Kilaru, M.S., Yaohua He, M.D., Ph.D., Puneet Mohan, M.D., Ph.D., Deepak L. Bhatt, M.D., M.P.H., Shaun Goodman, M.D., Freek W. Verheugt, M.D., Ph.D., Marcus Flather, M.D., Kurt Huber, M.D., Danny Liaw, M.D., Ph.D., Steen E. Husted, M.D., Jose Lopez-Sendon, M.D., Raffaele De Caterina, M.D., Petr Jansky, M.D., Harald Darius, M.D., Dragos Vinereanu, M.D., Jan H. Cornel, M.D., Frank Cools, M.D., Dan Atar, M.D., Jose Luis Leiva-Pons, M.D., Matyas Keltai, M.D., Hisao Ogawa, M.D., Ph.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Witold Ruzyllo, M.D., Rafael Diaz, M.D., Harvey White, M.D., Mikhail Ruda, M.D., Margarida Geraldes, Ph.D., Jack Lawrence, M.D., Robert A. Harrington, M.D., and Lars Wallentin, M.D., Ph.D., for the APPRAISE-2 Investigators*

ABSTRACT

BACKGROUND

Apixaban, an oral, direct factor Xa inhibitor, may reduce the risk of recurrent ischemic events when added to antiplatelet therapy after an acute coronary syndrome.

METHODS

We conducted a randomized, double-blind, placebo-controlled clinical trial comparing apixaban, at a dose of 5 mg twice daily, with placebo, in addition to standard antiplatelet therapy, in patients with a recent acute coronary syndrome and at least two additional risk factors for recurrent ischemic events.

RESULTS

The trial was terminated prematurely after recruitment of 7392 patients because of an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events. With a median follow-up of 241 days, the primary outcome of cardiovascular death, myocardial infarction, or ischemic stroke occurred in 279 of the 3705 patients (7.5%) assigned to apixaban (13.2 events per 100 patient-years) and in 293 of the 3687 patients (7.9%) assigned to placebo (14.0 events per 100 patient-years) (hazard ratio with apixaban, 0.95; 95% confidence interval [CI], 0.80 to 1.11; P=0.51). The primary safety outcome of major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) definition occurred in 46 of the 3673 patients (1.3%) who received at least one dose of apixaban (2.4 events per 100 patient-years) and in 18 of the 3642 patients (0.5%) who received at least one dose of placebo (0.9 events per 100 patient-years) (hazard ratio with apixaban, 2.59; 95% CI, 1.50 to 4.46; P=0.001). A greater number of intracranial and fatal bleeding events occurred with apixaban than with placebo.

CONCLUSIONS

The addition of apixaban, at a dose of 5 mg twice daily, to antiplatelet therapy in high-risk patients after an acute coronary syndrome increased the number of major bleeding events without a significant reduction in recurrent ischemic events. (Funded by Bristol-Myers Squibb and Pfizer; APPRAISE-2 ClinicalTrials.gov number, NCT00831441.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Alexander at Duke Clinical Research Institute, Duke University Medical Center, DUMC Box 3850, Durham, NC 27715, or at john.h.alexander@duke.edu.

*The investigators in the Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) trial are listed in the Supplementary Appendix, available at NEJM.org.

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Patients with acute coronary syndromes frequently have recurrent ischemic events despite the use of currently recommended antiplatelet therapy, revascularization procedures as appropriate, and other evidence-based secondary preventive measures.[1-3] Oral anticoagulation therapy with vitamin K antagonists reduces the incidence of recurrent ischemic events after myocardial infarction but also increases the risk of bleeding when it is added to aspirin or aspirin and clopidogrel.[4-9]

Apixaban, an orally active, selective, direct factor Xa inhibitor, has been shown to reduce the incidence of venous thromboembolism in patients undergoing orthopedic surgery and to prevent thromboembolic events in patients with atrial fibrillation who are not candidates for oral vitamin K antagonist therapy.[10-15] We previously studied the use of apixaban, at doses of 5 to 20 mg daily, in patients who had had recent acute coronary syndromes and who were receiving aspirin or aspirin plus clopidogrel.[16] Treatment with apixaban resulted in dose-related increases in bleeding events and a trend toward fewer ischemic events. Considering both ischemic events and bleeding events, the preferred dose was thought to be 10 mg daily. Similar findings were observed with another factor Xa inhibitor, rivaroxaban, in a similar population.[17] We therefore conducted a phase 3 trial to determine whether, in high-risk patients with an acute coronary syndrome, the benefit of apixaban in reducing ischemic events would outweigh the increased risk of bleeding.

Methods

Study Design

The Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) trial was a double-blind, placebo-controlled, randomized clinical trial conducted at 858 sites in 39 countries. The study was approved by the institutional review board at each participating site. All participating patients gave written informed consent. The trial was supervised by a steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) that included representatives from the sponsors (Bristol-Myers Squibb and Pfizer). The data were managed and all analyses were performed at the Duke Clinical Research Institute, Durham, North Carolina. All the authors designed the study, reviewed the data, participated in the analyses, and assume responsibility for the completeness and accuracy of the data and analyses and for the fidelity of the study to the protocol. The first author wrote the first draft of the manuscript, and all the authors provided comments on subsequent drafts and made the decision to submit the manuscript for publication. The trial protocol and statistical analysis plan are available at NEJM.org. The sponsors provided the drugs for the study.

Study Population

The main inclusion criterion for the trial was an acute coronary syndrome (myocardial infarction, with or without ST-segment elevation, or unstable angina) within the previous 7 days, with symptoms of myocardial ischemia lasting 10 minutes or more with the patient at rest plus either elevated levels of cardiac biomarkers or dynamic ST-segment depression or elevation of 0.1 mV or more. Patients who met this criterion were eligible for the study if their condition was clinically stable and they were receiving standard treatment after the acute coronary syndrome, including aspirin or aspirin plus any P2Y12-receptor antagonist. Eligible patients were also required to have two or more of the following high-risk characteristics: an age of at least 65 years, diabetes mellitus, myocardial infarction within the previous 5 years, cerebrovascular disease, peripheral vascular disease, clinical heart failure or a left ventricular ejection fraction of less than 40% in association with the index event, impaired renal function with a calculated creatinine clearance of less than 60 ml per minute, and no revascularization after the index event. Exclusion criteria are listed in the Supplementary Appendix.

Randomization and Study Regimen

Patients were randomly assigned, in a 1:1 ratio, to receive apixaban, at a dose of 5 mg twice daily, or matching placebo. Patients with an estimated creatinine clearance of less than 40 ml per minute at the time of randomization were randomly assigned to receive apixaban at a dose of 2.5 mg twice daily or matching placebo. Randomization was performed in a blinded fashion with the use of an interactive voice-response system, in permuted blocks of two, stratified according to site and according to planned long-term use of aspirin or aspirin plus a P2Y12-receptor antagonist. Patients who interrupted

the study regimen during the course of the trial were encouraged to resume taking the assigned drug if and when possible.

Investigators were encouraged to practice evidence-based medicine and follow appropriate clinical practice guidelines in managing the care of their patients. The use, choices, and duration of antiplatelet therapy, as well as decisions about the use of other medical treatments and subsequent revascularization procedures, were left to the discretion of the treating physicians.

STUDY OUTCOMES

The primary efficacy outcome was the composite of cardiovascular death, myocardial infarction, or ischemic stroke.[18] The primary safety outcome was major bleeding, according to the Thrombolysis in Myocardial Infarction (TIMI) definition.[19]

Prespecified secondary outcomes included the composite of cardiovascular death, myocardial infarction, ischemic stroke, or unstable angina; the composite of cardiovascular death, myocardial infarction, ischemic or hemorrhagic stroke, or fatal bleeding; and the composite of death from any cause, myocardial infarction, or ischemic or hemorrhagic stroke. Additional efficacy outcomes included the individual components of the primary efficacy outcome, unstable angina, and stent thrombosis.[20] Additional safety outcomes included TIMI major or minor bleeding, major or clinically relevant nonmajor bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) definitions, and severe or moderate bleeding according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) definitions.[21,22] Data on adverse events other than bleeding were also collected.

The primary and secondary efficacy outcomes and the main safety outcome were adjudicated with the use of prespecified criteria by an independent clinical events committee whose members were unaware of the group assignments. Detailed definitions of outcome events are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Assuming a recruitment period of approximately 2 years, an average follow-up period of 1.25 years, and a rate of the primary efficacy outcome of 8% per year, we estimated that we would need to enroll 10,800 patients to achieve the desired target of 938 patients with a primary efficacy outcome. With this number of patients with events, we estimated that the study would have 80% power to detect a 20% reduction in relative risk with apixaban as compared with placebo at a one-sided alpha level of 0.005 and 93% power to detect the same reduction in risk at a one-sided alpha level of 0.025.

In November 2010, after approximately 7000 patients had been recruited, the independent data monitoring committee recommended that the trial be stopped, owing to an excess of clinically important bleeding events with apixaban in the absence of a counterbalancing reduction in ischemic events. Recruitment was stopped on November 18, 2010. All the patients enrolled in the study were contacted and told to discontinue the study drug and schedule a final follow-up assessment. The trial database was locked on March 23, 2011.

The intended treatment period, starting on the day of randomization and ending at the efficacy cutoff date (November 18, 2010), is the basis for the efficacy analyses. The actual treatment period, starting on the date the first dose of study drug was administered and ending 2 days after the last dose of study drug was administered, is the basis for the analyses of safety. A post hoc analysis was performed to assess the primary efficacy outcome during the actual treatment period.

Efficacy and bleeding outcomes were analyzed with the use of a Cox proportional-hazards model that included the assigned study group as a covariate and that was stratified according to antiplatelet therapy (single or dual) at baseline. Data on patients who died of noncardiovascular causes were censored at the time of death. A point estimate and two-sided 95% confidence interval for the hazard ratio were calculated for each outcome. Prespecified efficacy and safety analyses were performed in subgroups according to baseline antiplatelet therapy, type of acute coronary syndrome, treatment for acute coronary syndrome, dose of apixaban, region, age, sex, race, body-mass index, degree of renal impairment, number of risk factors, presence or absence of diabetes mellitus, and presence or absence of heart failure. The rates of efficacy and bleeding events are reported as percentages and as events per 100 patient-years. Other categorical variables are reported as percentages. All P values are two-sided. All analyses were per-

formed with the use of SAS software, version 9.0 (SAS Institute).

RESULTS

STUDY PARTICIPANTS

A total of 7392 patients underwent randomization between March 17, 2009, and November 18, 2010 (Fig. 1 in the Supplementary Appendix). Patients underwent randomization a median of 6 days (interquartile range, 4 to 7) after the index event of acute coronary syndrome and 2 days (interquartile range, 2 to 4) after discontinuation of parenteral antithrombotic therapy. Among the patients who underwent randomization, 81 (1.1%) withdrew consent and 50 (0.7%) were lost to follow-up for the primary outcome during the intended treatment period. The median duration of follow-up from the time of randomization through the last date of contact in the study was 240 days (interquartile range, 132 to 352) among patients assigned to apixaban and 242 days (interquartile range, 131 to 352) among patients assigned to placebo.

By design, the trial population had high rates of diabetes, prior myocardial infarction, cerebrovascular and peripheral vascular disease, heart failure or left ventricular dysfunction, and impaired renal function, and a large proportion of the patients had not undergone revascularization for the index event (Table 1). More than half the patients had three or more protocol-defined high-risk characteristics at the time of enrollment.

The index event was a myocardial infarction with ST-segment elevation in approximately 40% of patients, a myocardial infarction without ST-segment elevation in 42%, and unstable angina in 18% (Table 1). More than 52% of the patients underwent coronary angiography, 44% underwent a percutaneous coronary intervention, and 55% had their condition managed medically.

At the time of randomization, nearly all the patients (97%) were taking aspirin. The majority of the patients (81%) were receiving aspirin plus a P2Y12-receptor antagonist, predominantly clopidogrel. Most patients were receiving other evidence-based therapies as well, and the rates of these therapies were similar in the apixaban and placebo groups.

STUDY DRUG AND ANTIPLATELET THERAPIES

A total of 7315 of the 7392 patients who underwent randomization (99.0%) received at least one dose of the assigned study drug; 8.5% of the patients were assigned to the reduced dose of apixaban or matching placebo. Of these 7315 patients, 863 of the 3673 patients who received at least one dose of apixaban (23.5%) and 746 of the 3642 who received at least one dose of placebo (20.5%) stopped taking the study drug before the end of the trial ($P=0.002$). The median exposure to the study drug was 175 days (interquartile range, 66 to 293) among patients receiving apixaban and 185 days (interquartile range, 75 to 298) among patients receiving placebo. The most common reasons for discontinuation of the study drug were adverse events (8.5% in the apixaban group vs. 6.5% in the placebo group) and withdrawal of consent (5.3% vs. 4.2%). A total of 1310 (21.5%) of the patients who were taking aspirin plus a P2Y12-receptor antagonist at the time of randomization stopped taking the P2Y12-receptor antagonist during the course of the trial, at a median of 39 days (interquartile range, 13 to 108) after randomization; 135 (11.1%) of the patients receiving aspirin alone at randomization started taking a P2Y12-receptor antagonist during the trial, at a median of 14 days (interquartile range, 4 to 93) after randomization.

EFFICACY OUTCOMES

The final number of primary efficacy events was 572, or 61.0% of the initially planned number. In the intention-to-treat analysis, the primary efficacy outcome of cardiovascular death, myocardial infarction, or ischemic stroke occurred in 279 patients (7.5%) assigned to apixaban (13.2 events per 100 patient-years) and in 293 patients (7.9%) assigned to placebo (14.0 events per 100 patient-years) (hazard ratio with apixaban, 0.95; 95% confidence interval [CI], 0.80 to 1.11; $P=0.51$) (Fig. 1 and Table 2). Similar results were seen in an on-treatment analysis (218 vs. 249 events; hazard ratio, 0.89; 95% CI, 0.74 to 1.06; $P=0.19$). There were also no significant differences between the apixaban and placebo groups with respect to any of the secondary efficacy outcomes (Table 2).

The effect of apixaban as compared with placebo was similar among patients receiving combination antiplatelet therapy and among those receiving aspirin alone. The rates of the primary efficacy outcome among patients who were receiving combination antiplatelet therapy were 7.2% in the apixaban group and 7.5% in the placebo group (hazard ratio with apixaban, 0.95; 95% CI, 0.79 to 1.15), and the corresponding rates among those receiving aspirin alone were 9.0% and 9.8%

Table 1. Baseline Characteristics of the Study Patients.*

Variable	Apixaban (N=3705)	Placebo (N=3687)
Demographic characteristics		
Age — yr		
Median	67	67
Interquartile range	59–73	58–74
Female sex — no. (%)	1209 (32.6)	1169 (31.7)
Risk factors specified as inclusion criteria — no. (%)†		
Age ≥65 yr	2179 (58.8)	2175 (59.0)
History of diabetes mellitus	1804 (48.7)	1732 (47.0)
Myocardial infarction within the previous 5 yr	923 (24.9)	1013 (27.5)
History of cerebrovascular disease	378 (10.2)	364 (9.9)
History of peripheral vascular disease	664 (17.9)	674 (18.3)
Heart failure or LVEF <40% associated with index ACS event	1489 (40.2)	1480 (40.1)
History of impaired renal function	1048 (28.3)	1089 (29.5)
No revascularization for index ACS event	2061 (55.6)	2034 (55.2)
Other medical history — no. (%)		
Heart failure	1023 (27.6)	1053 (28.6)
Prior coronary revascularization	1030 (27.8)	1060 (28.7)
Index ACS event		
Time from event to randomization — days		
Median	6.0	6.0
Interquartile range	4.0–7.0	4.0–7.0
Type of event — no. (%)		
ST-segment elevation myocardial infarction	1474 (39.8)	1453 (39.4)
Non–ST-segment elevation myocardial infarction	1533 (41.4)	1541 (41.8)
Unstable angina	673 (18.2)	667 (18.1)
Elevated cardiac markers — no. (%)‡	3007 (81.2)	2994 (81.2)
Management of event — no. (%)		
Coronary angiography	1923 (51.9)	1927 (52.3)
PCI	1624 (43.8)	1631 (44.2)
CABG	22 (0.6)	23 (0.6)
Medical therapy only	2061 (55.6)	2034 (55.2)
Use of parenteral antithrombotic agents — no. (%)	2972 (80.2)	2992 (81.1)
Selected medications — no. (%)		
Angiotensin-converting–enzyme inhibitor	2434 (65.7)	2406 (65.3)
Angiotensin-receptor blocker	527 (14.2)	503 (13.6)
Beta-blocker	2853 (77.0)	2816 (76.4)
Statin	3076 (83.0)	3105 (84.2)
Proton-pump inhibitor	894 (24.1)	906 (24.6)

* All baseline characteristics were well matched between the two groups (P>0.05). ACS denotes acute coronary syndrome, CABG coronary-artery bypass grafting, LVEF left ventricular ejection fraction, and PCI percutaneous coronary intervention.
† To be eligible for inclusion in the study, patients had to have two or more of these risk factors.
‡ The cardiac markers assessed included the MB fraction of creatine kinase and troponin T or I.

(hazard ratio, 0.92; 95% CI, 0.66 to 1.29) (P=0.87 for interaction). Similar findings with respect to the primary efficacy outcome were seen in all key subgroups (Fig. 2 in the Supplementary Appendix).

BLEEDING AND OTHER SAFETY OUTCOMES

In the on-treatment analysis, the primary safety outcome of TIMI major bleeding occurred in 46 of the 3673 patients (1.3%) who received at least

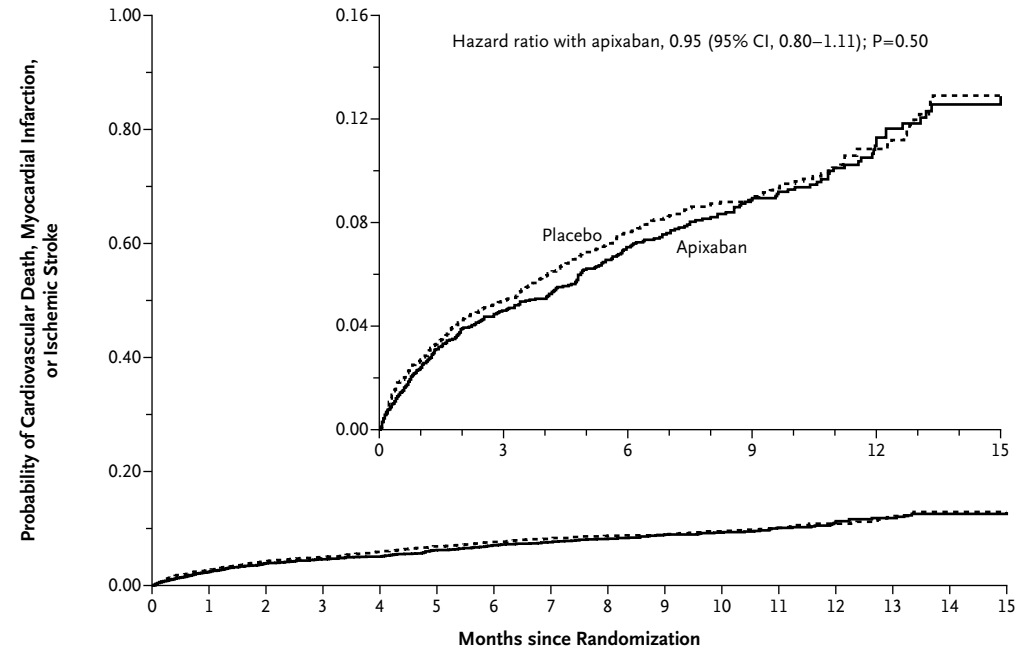


Figure 1. Kaplan–Meier Curves for the Primary Efficacy Outcome.

The primary efficacy outcome was the composite of cardiovascular death, myocardial infarction, or ischemic stroke. An intention-to-treat analysis was used to compare patients assigned to apixaban with those assigned to placebo. The inset shows the same data on an enlarged y axis.

one dose of apixaban (2.4 events per 100 patient-years), as compared with 18 of the 3642 patients (0.5%) who received at least one dose of placebo (0.9 events per 100 patient-years) (hazard ratio with apixaban, 2.59; 95% CI, 1.50 to 4.46; P=0.001) (Table 2 and Fig. 2). Among the patients receiving apixaban, as compared with those receiving placebo, there were more events of fatal bleeding (5 vs. 0), intracranial bleeding (12 vs. 3), ISTH major or clinically relevant nonmajor bleeding (117 vs. 45), and total bleeding (679 vs. 305). Patients receiving apixaban received more transfusions than did patients receiving placebo (144 [3.9%] vs. 73 [2.0%]).

The findings with respect to the primary safety outcome were consistent among all key subgroups (Fig. 3 in the Supplementary Appendix). The increase in bleeding events with apixaban, as compared with placebo, was seen both in patients taking combination antiplatelet therapy (1.3% vs. 0.6%; hazard ratio, 2.27; 95% CI, 1.28 to 4.02) and in patients taking aspirin alone (1.1% vs. 0.1%), although there was only a small number of major bleeding events in the aspirin-only subgroup.

The frequencies of serious adverse events and overall adverse events were similar in the apixaban group and the placebo group (24.3% and 59.0%, respectively, in the apixaban group and 24.3% and 57.7%, respectively, in the placebo group). The frequencies of events other than ischemic events and bleeding were either similar in the two groups or lower in the apixaban group than in the placebo group (Table 1 in the Supplementary Appendix). There were no significant between-group differences in the rates of adverse events related to hepatotoxicity.

DISCUSSION

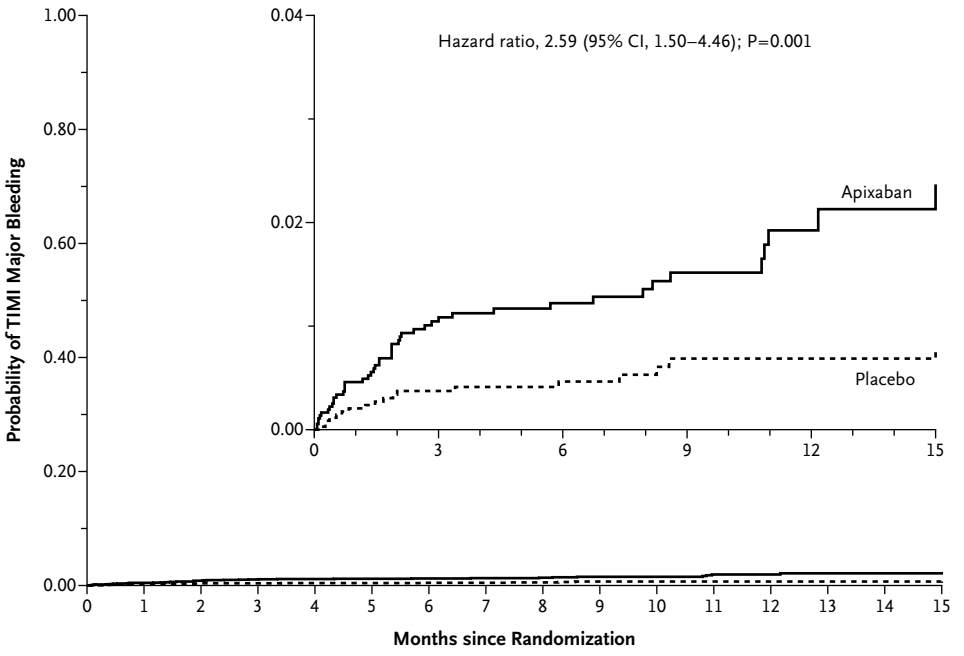
In this randomized clinical trial, the oral factor Xa inhibitor apixaban, administered at a dose of

Table 2. Clinical Outcomes.*

Outcome	Apixaban		Placebo		Hazard Ratio with Apixaban (95% CI)	P Value
	Total	Event Rate	Total	Event Rate		
	no. of patients (%)	*no. of events/ 100 patient-yr*	*no. of patients (%)*	*no. of events/ 100 patient-yr*		
Efficacy	3705 (100)		3687 (100)			
Cardiovascular death, myocardial infarction, or ischemic stroke	279 (7.5)	13.2	293 (7.9)	14.0	0.95 (0.80–1.11)	0.51
Cardiovascular death, myocardial infarction, ischemic stroke, or unstable angina	352 (9.5)	16.9	370 (10.0)	18.0	0.94 (0.82–1.09)	0.43
Death	155 (4.2)	7.1	143 (3.9)	6.6	1.08 (0.86–1.35)	0.51
Cardiovascular death	105 (2.8)	4.8	109 (3.0)	5.0	0.96 (0.73–1.25)	0.76
Myocardial infarction	182 (4.9)	8.6	194 (5.3)	9.2	0.93 (0.76–1.14)	0.51
Ischemic stroke	23 (0.6)	1.1	34 (0.9)	1.6	0.68 (0.40–1.15)	0.14
Unstable angina	85 (2.3)	4.0	90 (2.4)	4.2	0.94 (0.70–1.26)	0.67
Stent thrombosis	35 (0.9)	1.6	48 (1.3)	2.2	0.73 (0.47–1.12)	0.15
Safety: bleeding†	3673 (100)		3642 (100)			
TIMI criteria						
Major bleeding	46 (1.3)	2.4	18 (0.5)	0.9	2.59 (1.50–4.46)	0.001
Major or minor bleeding	80 (2.2)	4.2	29 (0.8)	1.5	2.79 (1.83–4.27)	<0.001
ISTH criteria						
Major bleeding	98 (2.7)	5.1	40 (1.1)	2.0	2.48 (1.72–3.58)	<0.001
Major or clinically relevant nonmajor bleeding	117 (3.2)	6.2	45 (1.2)	2.3	2.64 (1.87–3.72)	<0.001
GUSTO criteria						
Severe bleeding	36 (1.0)	1.8	12 (0.3)	0.6	3.05 (1.59–5.86)	0.001
Severe or moderate bleeding	83 (2.3)	4.3	25 (0.7)	1.3	3.37 (2.16–5.27)	<0.001
Fatal bleeding	5 (0.1)	0.3	0	NA	NA	NA
Intracranial bleeding	12 (0.3)	0.6	3 (0.1)	0.2	4.06 (1.15–14.38)	0.03
Any bleeding	679 (18.5)	40.1	305 (8.4)	14.4	2.36 (2.06–2.70)	<0.001
Net clinical outcomes	3705 (100)		3687 (100)			
Cardiovascular death, myocardial infarction, ischemic or hemorrhagic stroke, or fatal bleeding	295 (8.0)	14.0	299 (8.1)	14.3	0.98 (0.83–1.15)	0.80
Death, myocardial infarction, or ischemic or hemorrhagic stroke	327 (8.8)	15.5	328 (8.9)	15.6	0.99 (0.85, 1.15)	0.90

* GUSTO denotes Global Use of Strategies to Open Occluded Coronary Arteries, ISTH International Society on Thrombosis and Haemostasis, NA not applicable, and TIMI Thrombolysis in Myocardial Infarction.
† The safety outcomes were assessed in an analysis of data from patients who received at least one dose of the study drug.

5 mg twice daily in high-risk patients who were taking either aspirin or aspirin plus clopidogrel after an acute coronary syndrome, resulted in a significant increase in bleeding events, including increases in events of fatal and intracranial bleeding, without a significant reduction in recurrent ischemic events. These findings were consistent in all subgroups, including subgroups defined according to antiplatelet therapy (aspirin plus clopidogrel vs. aspirin alone) and according to management of the acute coronary syndrome (revascularization vs. noninvasive management). The increase in bleeding with apixaban led more frequently to discontinuation of the study drug and resulted in the pre-



No. at Risk

Apixaban	3672	3187	2815	2558	2264	2063	1794	1517	1326	1104	884	698	506	344	225	143
Placebo	3643	3178	2881	2600	2339	2133	1884	1573	1369	1137	905	734	532	380	240	151

Figure 2. Kaplan–Meier Curves for the Primary Safety Outcome.

The primary safety outcome was major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) definition. An on-treatment analysis was used to compare patients who received at least one dose of apixaban with those who received at least one dose of placebo. The inset shows the same data on an enlarged y axis.

mature termination of the trial — both of which limit the certainty of the conclusions that can be drawn about efficacy.

The current standard of care for patients after an acute coronary syndrome includes dual antiplatelet therapy, typically with aspirin and clopidogrel.[23,27] Despite aggressive use of dual antiplatelet therapy, however, patients frequently have recurrent ischemic events. Newer, more potent P2Y12-receptor antagonists provide additional reductions in ischemic events[2] and mortality[3] but at the cost of an increase in bleeding. Thus, patients with a substantial risk of recurrent events have an important unmet need for better secondary prevention.[28] A combination of antiplatelet and anticoagulant agents seems to be an attractive approach. However, such broad antithrombotic therapy may also pose an unacceptable risk of bleeding.[7,29]

In this trial, we enrolled a high-risk patient population, with large proportions of patients who had diabetes, heart failure, or renal insufficiency, as well as a large proportion of patients who did not undergo revascularization for the index event.[2,3,22,30-34] We hypothesized that this population was most likely to benefit from the addition of an oral anticoagulant agent in addition to standard antiplatelet and other evidence-based therapies. Further investigation is required to determine whether there are other patient populations for which the results may be different or concomitant interventions that might change the risk–benefit profile of the combination of anticoagulation plus antiplatelet therapy in this population.

Three phase 2 clinical trials have investigated the use of new oral anticoagulant drugs in addition to contemporary antiplatelet therapy in patients who have had a recent acute coronary syndrome.[16,17,35] When added to antiplatelet therapy, both apixaban and rivaroxaban resulted in dose-related increases in bleeding but also appeared to result in larger absolute reductions in ischemic events than those seen with placebo. The increases in bleeding were smaller and the reductions in ischemic events were more pronounced

among patients taking aspirin alone than among those taking aspirin plus clopidogrel. The findings from the APPRAISE-2 trial definitively confirm the increases in bleeding observed in the phase 2 trials of factor Xa inhibitors administered in addition to antiplatelet therapy. Unfortunately, the reductions in ischemic events suggested in the phase 2 trial were not observed in this larger phase 3 trial. Because this trial was stopped early owing to the increase in bleeding events, with fewer ischemic events having occurred than the number planned, uncertainty remains regarding the effect of apixaban on ischemic events. The ATLAS-ACS 2 TIMI 51 trial (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51; ClinicalTrials.gov number, NCT00402597), which includes a lower-risk population than that in the APPRAISE-2 trial and is evaluating two different doses of another factor Xa inhibitor, is currently ongoing.[36] Whether this trial will have similar results remains to be seen.

Meta-analyses of earlier studies with oral vitamin K antagonists combined with aspirin, as compared with aspirin alone, showed that there were reductions in recurrent ischemic events in patients after acute coronary syndromes.[4,5] In a large, observational analysis that included more than 40,000 patients with myocardial infarction, the use of triple therapy (aspirin, clopidogrel, and a vitamin K antagonist), as compared with aspirin alone, was associated with a rate of bleeding that was increased by a factor of 4, with no significant difference in the rate of survival.[29] Similar increases in bleeding events have been seen in other studies and other clinical settings in which the use of combined antiplatelet and anticoagulant therapy may be considered.[7] The results of the current trial raise doubt about whether meaningful incremental efficacy can be achieved with an acceptable risk of bleeding by combining a long-term oral anticoagulant with both aspirin and a P2Y12-receptor antagonist in patients with coronary disease.

In summary, we evaluated the addition of apixaban, at a dose of 5 mg twice daily, to standard antiplatelet therapy in patients with an acute coronary syndrome. Treatment with apixaban, as compared with placebo, was associated with a significant increase in the risk of bleeding, without a significant effect on the incidence of recurrent ischemic events.

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APPENDIX

The authors' affiliations are as follows: Duke Clinical Research Institute, Duke University Medical Center, Durham, NC (J.H.A., R.D.L., R.K., R.A.H.); Uppsala Clinical Research Center, Uppsala, Sweden (S.J., L.W.); Bristol-Myers Squibb, Princeton, NJ (Y.H., P.M., D.L., M.G., J.L.); Brigham and Women's Hospital and the Veterans Affairs Boston Healthcare System, Boston (D.L.B.); Canadian Heart Research Center, Toronto (S.G.); Onze Lieve Vrouwe Gasthuis, Amsterdam (F.W.V.); Clinical Trials and Evaluation Unit, Royal Brompton Hospital and Harefield NHS Foundation Trust, London (M.F.); Wilhelminenspital, Vienna (K.H.); the Department of Cardiology and Medicine A, Aarhus Amtssygehus, Aarhus University Hospital, Aarhus, Denmark (S.E.H.); Hospital Universitario La Paz, Madrid (J.L.-S.); Institute of Cardiology and University Cardiology Division, G. d'Annunzio University, Chieti, Italy (R.D.C.); Motol University Hospital, Prague, Czech Republic (P.J.); Neukoelln Medical Center, Berlin (H.D.); University Hospital of Bucharest, Bucharest, Romania (D.V.); Medical Center Alkmaar, Alkmaar, the Netherlands (J.H.C.); Academisch Ziekenhuis Klina, Brasschaat, Belgium (F.C.); Oslo University Hospital, Oslo (D.A.); Hospital Central Dr. Ignacio Morones Prieto, San Luis Potosi, Mexico (J.L.L.-P.); Hungarian Institute of Cardiology, Budapest, Hungary (M.K.); Kumamoto University, Kumamoto, Japan (H.O.); St. John's Medical College, Bangalore, India (P.P.); Institute of Cardiology, Kiev, Ukraine (A.P.); Institute of Cardiology, Warsaw, Poland (W.R.); ECLA Estudios Cardiológicos Latinoamérica, Rosario, Argentina (R.D.); Green Lane Cardiovascular Research Unit, Auckland City Hospital, Auckland, New Zealand (H.W.); and Cardiology Research Center, Moscow (M.R.).

REFERENCES

1. Lewis BS, Mehta SR, Fox KA, et al. Benefit of clopidogrel according to timing of percutaneous coronary intervention in patients with acute coronary syndromes: further results from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Am Heart J 2005;150:1177-84.
2. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.
3. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.
4. Rothberg MB, Celestin C, Fiore LD, Lawler E, Cook JR. Warfarin plus aspirin after myocardial infarction or the acute coronary syndrome: meta-analysis with estimates of risk and benefit. Ann Intern Med 2005;143:241-50.
5. Andreotti F, Testa L, Biondi-Zoccai GG, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. Eur Heart J 2006;27:519-26.
6. Karjalainen PP, Porela P, Ylitalo A, et al. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. Eur Heart J 2007;28:726-32.
7. Hansen ML, Sørensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med 2010;170:1433-41.
8. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347:969-74.
9. van Es RF, Jonker JJ, Verheugt FW,

Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet 2002;360:109-13.
10. Wong PC, Crain EJ, Xin B, et al. Apixaban, an oral, direct and highly selective factor Xa inhibitor: in vitro, antithrombotic and antihemostatic studies. J Thromb Haemost 2008;6:820-9.
11. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med 2009; 361:594-604. [Erratum, N Engl J Med 2009; 361:1814.]
12. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010;375:807-15.
13. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med 2010;363:2487-98.
14. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011;364:806-17.
15. Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. J Thromb Haemost 2007;5: 2368-75.
16. Alexander JH, Becker RC, Bhatt DL, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation 2009;119: 2877-85.
17. Mega JL, Braunwald E, Mohanavelu S, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet 2009;374:29-38.
18. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol 2007;50:2173-95.
19. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase: clinical findings through hospital discharge. Circulation 1987;76:142-54.
20. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
21. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.
22. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329: 673-82.
23. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324:71-86. [Erratum, BMJ 2002;324:141.]
24. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502. [Errata, N Engl J Med 2001;345:1506, 1716.]
25. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527-33.
26. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol 2007;50(7):e1-e157.
27. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28: 1598-660.
28. Fox KA, Carruthers KF, Dunbar DR, et al. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). Eur Heart J 2010;31:2755-64.
29. Sørensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet 2009;374:1967-74.
30. APEX AMI Investigators, Armstrong PW, Granger CB, et al. Pexelizumab for acute ST-elevation myocardial infarction in patients undergoing primary percutaneous coronary intervention: a randomized controlled trial. JAMA 2007;297:43-51.
31. Ferguson JJ, Califf RM, Antman EM, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. JAMA 2004;292:45-54.
32. Giugliano RP, White JA, Bode C, et al. Early versus delayed, provisional eptifibatide in acute coronary syndromes. N Engl J Med 2009;360:2176-90.
33. Bhatt DL, Roe MT, Peterson ED, et al. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. JAMA 2004; 292:2096-104.
34. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ 2006;333: 1091-4.
35. Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J 2011 May 7 (Epub ahead of print).
36. Gibson CM, Mega JL, Burton P, et al. Rationale and design of the Anti-Xa Therapy to Lower cardiovascular events in Addition to standard therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS-ACS 2 TIMI 51) trial: a randomized, double-blind, placebo controlled study to evaluate the efficacy and safety of rivaroxaban in subjects with acute coronary syndrome. Am Heart J 2011;161(5):815.e6-821.e6.